The dream of preventing cancer with a vitamin pill is rapidly evaporating. Over the past few months, results from clinical trials and observational studies report no benefit—and in a few cases, possible harm—from supplementation with several micronutrients, including vitamins C, D, and E; selenium; calcium; and folate.

The findings have sobered investigators in the field of chemoprevention and led to a wholesale reevaluation of the methods used to assess possible benefits of vitamins and minerals and to prioritize them for definitive testing.

“I think there is a lot of disappointment,” said Peter Gann, M.D., Sc.D., a physician–epidemiologist at the University of Illinois at Chicago who studies nutrition and cancer. “When these expensive trials were being designed, there was a lot of hope. Some pretty heavy bets were being placed on those interventions.”

In light of the results, investigators anticipate more laboratory work and smaller, exploratory human studies designed to probe exactly how vitamins and minerals affect tumor formation and growth. They also foresee more research geared toward determining whether certain subpopulations—say, those with a certain genetic profile—might still benefit from supplementation.

But for preventing cancer in the general population, the prospects look bleaker than ever. “Almost unbelievably, none of the studies has shown a benefit, and a couple even suggest the potential for harm,” said Philip Taylor, M.D., Sc.D., of the National Cancer Institute’s Genetic Epidemiology Branch. “Given these results, it’s hard to be encouraged about micronutrient trials in well-nourished Western populations.”

However, there is one bright spot. As reported in this issue of the Journal, a study led by Taylor and conducted in China found that a supplement containing selenium, vitamin E, and β-carotene reduced mortality from gastric cancer. Moreover, the benefit continued for 10 years after the volunteers stopped taking the supplement. “This represents the longest durability of efficacy observed ... in any prevention trial, including drug trials,” Taylor said. But he and others point out that the study population, in remote Linxian, China, ate a poor diet and most likely suffered deficiencies of the nutrients tested.

“It may be that with the people of Linxian you tipped them into a relatively normal range” of the target micronutrients, said John Potter, M.D., Ph.D., a senior advisor to the Fred Hutchinson Cancer Research Center in Seattle who studies nutrition and cancer, “whereas in the U.S. populations you’re dealing with people who by and large have adequate amounts of these things.”

<table>
<thead>
<tr>
<th>Micronutrients tested</th>
<th>Against which cancers</th>
<th>Outcome</th>
<th>Study type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium</td>
<td>Prostate</td>
<td>No effect</td>
<td>Prospective intervention (SELECT)</td>
<td>Lippman et al., JAMA, Jan. 2009</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>All cancers in men</td>
<td>No effect</td>
<td>Prospective intervention (Physicians’ Health Study II)</td>
<td>Gaziano et al., JAMA, Jan. 2009</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Prostate, all cancers in men</td>
<td>No Effect</td>
<td>Prospective intervention, two trials (SELECT and Physicians’ Health Study II)</td>
<td>Lippman et al. Gaziano et al., JAMA, Jan. 2009</td>
</tr>
<tr>
<td>Calcium + vitamin D</td>
<td>Breast in women</td>
<td>No effect</td>
<td>Prospective observational (WHI)</td>
<td>Chlebowski et al., JNCI, Nov. 2008</td>
</tr>
<tr>
<td>Folate</td>
<td>Prostate</td>
<td>More incidence</td>
<td>Prospective intervention (Aspirin/Folate Polyp Prevention Study)</td>
<td>Figueiredo et al., JNCI, March 2009</td>
</tr>
<tr>
<td>Selenium + vitamin E + β-carotene</td>
<td>Gastric</td>
<td>Fewer deaths</td>
<td>Prospective intervention (Linxian Nutrition Intervention Trial)</td>
<td>Qiao et al., JNCI, April 2009</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Prostate</td>
<td>No effect</td>
<td>Case–control (PLCO Cancer Screening Trial)</td>
<td>Ahn et al., JNCI, June 2008</td>
</tr>
<tr>
<td>Folate + vitamin B₉ + vitamin B₁₂</td>
<td>Breast in women, all cancers in women</td>
<td>No effect</td>
<td>Prospective intervention (WAFACS trial)</td>
<td>Zhang et al., JAMA, Nov. 2008</td>
</tr>
</tbody>
</table>
Slew of Results

Of the recent studies (see table), the heaviest bet was placed on SELECT, a randomized clinical trial of 35,000 men to test vitamin E and selenium for the prevention of prostate cancer. Funded mostly by the NCI, the trial cost $120 million and took nearly a decade. Last fall, SELECT’s data safety and monitoring committee concluded that neither compound helped prevent prostate cancer and told participants to stop taking their pills.

Another randomized trial, the Physicians’ Health Study II, also found no reduction in incidence of prostate cancer or total cancer among men taking vitamin E. Also, the 14,000-man study, published in January, found that vitamin C did not reduce incidence of prostate cancer or total cancer. And in a secondary epidemiologic analysis of the long-running Prostate, Lung, Colon, and Ovarian Cancer Screening Trial, published last June, vitamin D also proved ineffective for preventing prostate cancer.

The news is just as meager for women. In November, the Women’s Health Initiative (WHI), a randomized trial of 36,000 postmenopausal women, reported that neither calcium nor vitamin D helped prevent breast cancer. In February, an observational component of the WHI showed that multivitamin use did not affect breast or total cancer incidence. Also, the 14,000-man study, published last June, found that vitamin D also proved ineffective for preventing prostate cancer.

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“Most of us thought if you supply enough selenium, regardless of form ... you’ll get the same response,” said Milner. “I still somewhat believe that.” But, because of the lack of data, “none of [the explanations] are very satisfying,” he said.

As for timing, animal studies suggest that a dose of the right vitamins and minerals may indeed help prevent new cancers, but only if given early enough. If the nutrient boost arrives after a preneoplastic lesion forms, it may be too late. In fact, certain nutrients may actually accelerate tumor growth, Milner said.

Some of the new findings support this notion. The first report from SELECT,
published in January, highlighted a non-statistically significant increase in prostate cancers among men who took vitamin E. Over 5 years, 4.93% taking vitamin E developed prostate cancer, compared with 4.36% among those taking placebo. Another randomized trial, the Aspirin/Folate Polyp Prevention Study, found a statistically significant excess of prostate cancers in the men who received folic acid, a form of folate. Over 10 years, 9.7% of men taking folic acid developed prostate cancer, contrasted with 3.3% in the placebo group. And going back to the late 1990s, two other randomized studies showed that supplements of β-carotene, a form of vitamin A, increased the risk of lung cancer in smokers.

The emerging picture is complex. “Folate deficiency increases cancer risk, and excess folate also increases cancer risk. We know that,” said Milner. “We also have some evidence with calcium, with vitamin B, with selenium, certainly historically with β-carotene. At low ends there may be some benefits, but too much is a harm.”

Potter, who has long opposed large single- or dual-agent chemoprevention cancer trials, said, “If you look at a lot of the trials we’ve done, we’ve used [high] doses on the basis that if some is good, more is better.” But, he pointed out, the findings from the Linxian trial suggest that, instead, a “physiologic” dose—something close to the U.S. Department of Agriculture’s recommended daily intake—may be optimal. Or, as Milner put it: “Too much of a good thing isn’t necessarily good, is it?”

Rethinking Study Design
In the wake of the findings, researchers expect no new large studies of vitamins and minerals for cancer prevention. “It’s going to be very hard for somebody to get financial support for a large phase III trial,” said Gann.

Instead, the field is refocusing on a personalized approach, said Milner, and trying to understand the individual differences in how people process vitamins and minerals.

“I think the area of genetics and personalized medicine is really going to advance this field,” said Mara Vitolins, Ph.D., the principal investigator for the WHI at Wake Forest University. She gives one hypothetical example: Research may uncover that some people carry a gene variant that hinders absorption of folic acid from food. Those people might then benefit from a supplement.

The results also are pushing researchers to return to where the nutrients of interest originate—food. This idea harks back to early epidemiologic studies that showed an association between diet and cancer rates.

“The reality may be that the beneficial effects of diet that we see pretty consistently in epidemiologic research are not
attributable to single compounds but may be attributable to consumption of whole foods or even patterns of foods,” said Gann.

Potter said, “We need to rethink what we’re doing. Vegetables are this incredibly complex mix of all these compounds, and yet we insist on trying to isolate a single agent from them.”

For antioxidants, which include vitamins C and E, “there are hard lessons here, and I don’t think people will be so inclined to try to isolate a single one and give it in large doses,” said Gann. Oxidative stress has a positive function in the body too, he pointed out, such as helping to combat infections.

In a recent editorial accompanying the folate study (see J. Natl. Cancer Inst. 2009;101:363–5), Alan Kristal, Dr.P.H., from Fred Hutchinson Cancer Research Center, and Scott Lippman, M.D., from the University of Texas M. D. Anderson Cancer Center in Houston, suggest small dietary cohort studies with more accurate food intake assessment than that provided by the questionnaires typically used. They also point to a study they are conducting to unravel how components in broccoli might affect early development of prostate cancer. If the study shows that large amounts of broccoli do influence prostate tumor formation, then a larger trial of the components should move forward, they say, noting that such a model provides a more solid footing for large clinical trials of nutrients.

Potter advocates observational studies of diet that focus on the mechanisms of nutrients. And like Kristal and Lippman, he also wants small-scale intervention trials that focus on gene–nutrient and nutrient–nutrient interactions in the body—that is, studies that sort out exactly what happens when a person takes five or 10 times the recommended daily intake of a vitamin or mineral.

“These are really important steps to take right now,” said Potter. “We’ve got to work out the complexity of the whole issue.”